THE CAMMIDGE REACTION IN EXPERIMENTAL LESIONS OF THE PANCREAS.[1]

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Although abundant clinical proof has been afforded his reaction by Cammidge, it has thus far remained for others to publish results of work conducted along the fundamental lines of chemistry and experimentation. Reports of experimental studies have by no means kept pace with those derived from clinical observation, which is the more to be regretted since the value which would accrue from the establishment of a diagnostic measure in pancreatic disease is inestimable and demands a firm experimental basis before it can be accepted.

In a preliminary report[2] we published results of some studies of the Cammidge reaction in experimental pancreatitis, using the "C" reaction, which had given good clinical results in the hands of one of us.[3] Up to that time no report of experimental work had appeared in which this modified reaction had been used, but since our first report Eichler and Schirokauer[4] have published results of some experimentation in dogs, using the "C" method. Their work has left them somewhat in doubt as to the usefulness of the test, the crystals appearing at irregular intervals even when definite pancreatic lesions existed.

The work which we report at this time was undertaken to confirm or to refute Cammidge's claims, that by means of chemical analysis a specific substance could be demonstrated in the urine of individuals suffering with pancreatic disease. This specific substance was thought by Cammidge to be glycerin, absorbed into the circulation during the process of fat necrosis and excreted finally in the urine. This hypothesis was soon abandoned for the present belief that the substance which is isolated by means of phenylhydrazin is a pentose, not found as such in the urine, but obtained from some mother substance by hydrolysis with hydrochloric acid. What this mother substance may be is not stated, but its origin is thought to be from the pancreas, which, as is well known, contains a relatively large amount (2.48 per cent.) of pentose-yielding material.

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[1] Read at a meeting of the Association of American Physicians, Washington, D. C., May 11 and 12, 1909.

[2] Amer. Jour. Med. Sci., January, 1909.

[3] Annals of Surgery, February, 1909.

[4] Berl. klin. Woch., 1909, p. 352.

We have endeavored in our series of cases to imitate the acute and chronic types of pancreatitis met with in human beings. The first is easily done by the injection of oil into the pancreatic duct, while the morbid changes seen in the second type of pancreatic lesion were closely simulated by simple ligation of the duct of Wirsung. All of our experimental animals were dogs, and before operation they were confined for from one to more days in a cage used for metabolic studies. The food consisted of meat, potatoes, bread, and water. The urine was collected for twenty-four hours preceding operation, and in every instance, with the exception of three of our early animals, it was examined for albumin, sugar, and the Cammidge reaction. Albumin was tested for by the Heller's test, and if present was removed by heat and acid. Sugar was tested for by Fehling's and Nylander's methods, and the Cammidge reaction was performed according to the directions given in Robson and Cammidge's book.[5] This is the so-called "C" reaction. It may be stated parenthetically that albumin was almost a constant constituent of the dogs' urines; sugar was never found before, and with the exception of our extirpation series, never after operation; and the Cammidge reaction was found but once before operation, this dog, of course, being discarded as valueless in our experiments.

Operation was performed under aseptic conditions, ether being used as an anesthetic. Postoperative suppuration was never seen, although no dressing or protection was given the wound. The urine obtained after operation was examined for albumin, sugar, and for the Cammidge reaction. Seventeen dogs were studied—six for acute pancreatitis, four for the effects following ligation, two for the effects following extirpation of half of the pancreas (tail), three for the effects following crushing of the tail of the pancreas, and in two dogs a total extirpation was performed.

Series I.—The pancreatic lesions in this series were induced by the injection of from 10 to 30 c.c. of cotton-seed oil into the pancreatic duct, a procedure which causes rapid necrosis of the pancreas.

Dog 1. The urine before operation was not examined. The dog was killed eight hours after operation, and the urine collected up to that time gave a positive reaction. Macroscopic examination of the pancreas showed a diffuse necrotic process which involved most of the organ. A microscopic study revealed complete destruction of the tissue.

Dog 2. The urine before operation showed no Cammidge reaction. The dog was killed eight hours after operation, and the urine failed to show a positive reaction. The pathological examination of the pancreas showed neither macroscopic nor microscopic lesions, as the attempt to inject oil into the pancreatic duct had been unsuccessful.

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[5] The Pancreas, its Surgery and Pathology. 1907.

Dog 3. The urine before operation was not examined. The dog was killed eight hours after operation, and the urine collected up to that time showed a positive reaction. The postmortem examination of the pancreas revealed a diffuse necrotic process; lesions similar in nature were seen microscopically.

Dog 4. The urine before operation showed no Cammidge crystals. The urine after operation gave a positive reaction. The dog was killed eight hours after operation, and the macroscopic and microscopic examination of the pancreas showed a diffuse necrotic process.

Dog 5. The urine before operation was not examined. The urine after operation gave a positive reaction. The animal was killed eight hours after operation, and the pancreas was found to be necrotic except at the tail. Microscopic examination of the head revealed complete necrosis of the tissue, with hemorrhagic and leukocytic infiltration. In the tail there was marked parenchymatous degeneration and a few areas of necrosis.

Dog 6. The urine before operation showed no Cammidge reaction. The urine the first hour after operation was negative; four hours after operation it was positive. The dog was killed at this time, and the usual necrotic appearance following oil injections was seen. On microscopic examination, normal tissue was nowhere visible except in the tail.

Series II.—The pancreatic lesions in this series were caused by ligation of the pancreatic duct.

Dog 7. The urine before operation was negative for the Cammidge reaction; the urine the first day after operation was negative; the urine the second day after operation gave a positive reaction; on the third, fourth, and fifth days, positive reactions were obtained. The dog was killed seven days after operation, and an area of induration was found in the head of the pancreas opposite the point of ligation. The lesion, which was the size of a large walnut, was distinctly hard, and cut with greater resistance than the remaining portions of the gland. Microscopic study of the indurated tissue showed a subacute inflammatory process, which had caused small areas of necrosis in the acini. A leukocytic infiltration, consisting for the most part of round cells, was seen in the stroma and, to a less extent, about the acini. Proliferated connective tissue cells were also noted.

Dog 8. The urine before operation showed no Cammidge reaction. Positive reactions were obtained on the first and second days following operation. The dog was killed on the second day, and the pancreas was found to be indurated in an area about the size and shape of a hickory nut, the lesion being directly above the ligature, which still surrounded the duct. Microscopic examination revealed changes similar to those seen in the preceding case, but not so extensive.

Dog 9. The urine before operation was negative for the Cammidge reaction. Negative reactions were obtained on the second, third, and fourth days following operation. On the fifth and sixth days after operation an attempt was made to open the pancreatic duct at the point of ligation, but was unsuccessful, owing to the induration about the duct. The first day after the second operation the urine was lost; on the second and third days the reaction was negative. On the fourth day typical crystals were found, and on that day the dog died. The urine collected on this day up to the time of death gave a negative reaction. Owing to advanced decomposition the pancreas was not examined microscopically. We are unable to explain the irregularity in the appearance of the crystals in this case.

Dog 10. The urine before operation was not examined. The first day after operation it was negative, but positive reactions were obtained on the second and third days. On the third day the duct was again exposed, the ligature cut, and the intestine opened. A probe was inserted in the duct and a point of resistance was encountered 1 cm. from the ampulla. Gentle pressure overcame the resistance and the probe was advanced still farther. On withdrawing it the same resistance was again met with. The head of the pancreas felt decidedly indurated. The urine following this second operation was so scanty that it could not be examined. On the second and third days negative reactions were obtained; on the fourth day a positive reaction, on the fifth a negative, on the sixth and seventh days positive reactions, and thereafter negative reactions were obtained. On the fifteenth day after the first operation, or twelve days after the second operation, the abdomen was again opened, and the omentum was found to be so adherent that it was impossible to locate the pancreatic duct. The dog was killed five days later, or on the twentieth day after the first operation; the pancreas was very much indurated and the duct could not be found. A microscopic examination was not made.

SERIES III.—In this series the tail of the pancreas was extirpated to a point immediately below the pancreatic duct.

Dog 11. The urine before operation gave no Cammidge reaction. The day following operation no reaction was obtained, but on the second day typical crystals were seen. The animal died three days after operation, and the autopsy disclosed a necrotic condition of the pancreas. The duct was found to have been ligated, so that this case can not be properly regarded as an example of the results following partial extirpation, but rather as an instance of incomplete extirpation plus ligation. Microscopic sections from the head of the pancreas showed well-preserved cells, the nuclei being slightly obscured by cloudy swelling. Small areas of liquefaction necrosis were seen, and considerable hemorrhage was present in the tissues.

Dog 12. Urine before operation was negative. No pancreatic reaction was obtained on the first, second, third, fourth, fifth, and sixth days. Thereafter, until the nineteenth day, positive reactions were found. On that day the dog was allowed to run out of doors, and through carelessness the animal escaped. Examination of the excised portion of pancreas revealed a normal gland.

SERIES IV.—In all the cases in this series the tail of the pancreas was crushed with a hemostat in six places.

Dog 13. The urine before operation was negative. On the first, second, third, fourth, and fifth days positive pancreatic reactions were obtained. The dog was killed six days after the operation. The pancreas showed induration of the head and some injection about the tail, but no fat necrosis was apparent. Microscopic examination of the head of the pancreas showed some increase of connective tissue around the acini. The parenchyma seemed normal in appearance.

Dog 14. The urine before operation was negative. No urine was obtained the first day after operation. On the second day the urine was negative, but on the third and fourth days positive reactions were obtained. The dog was killed on the fifth day after operation. The tail of the pancreas was hemorrhagic and necrotic. The head was slightly indurated, the duct patulous. On microscopic examination the tail showed advanced necrosis of the cells, the head being practically normal.

Dog 15. The urine before operation was negative. Up to the sixth day after operation no Cammidge reaction was obtained; on the sixth and seventh days positive crystals were seen. The urine was not studied again until nineteen days after operation, when it was negative for the pancreatic reaction. Two days later, when we intended to kill the animal for the purpose of macroscopic and microscopic examination of the pancreas, we found that the dog had been removed from the cage and had been disposed of, so a pathological report on this case cannot be made.

SERIES V.—In this series a total extirpation was attempted.

Dog 16. The urine before operation was negative. The animal died the day following operation, and the urine collected up to that time gave a positive pancreatic reaction. Examination of the pancreas revealed a normal condition of that gland.

Dog 17. The urine before operation was negative. On the first and second days after operation positive reactions were obtained. The animal died on the second day. The pancreas seemed normal on microscopic examination.

We were led to believe from the results obtained in Series I, and from those seen in Dogs 7 and 8 (Series II), that occlusion of the pancreatic duct was the principal causative factor in the production of the Cammidge reaction. We tried to establish this fact by removing the obstruction in the remaining two dogs of the second series, but were unsuccessful in Dog 9, and in Dog 10 positive reactions were obtained after two negative days. This may have been caused by a closure of the duct, but we have no means of verification, as there were so many adhesions that the pancreatic duct could not be located.

The view that occlusion of the duct might be the main cause of the appearance of Cammidge crystals had to be abandoned after we had completed Series III and IV, as the duct was left patulous in these cases, except in Dog 11 (Series III), and positive reactions were obtained in each case.

Cammidge has asserted that pentose is the specific substance which he isolates from the urine by his method, and that the pentose has its origin in the pancreas. We are not in favor of this view, for, were this correct, we should not expect to find typical crystals after total extirpation of the gland. We are inclined to believe that the substance found by the use of Cammidge's technique is but an expression of disturbed carbohydrate metabolism, this disturbance being referable to morbid changes in the pancreas. We have made no investigations along the lines of chemistry, but the melting point of the crystals found in one case was between 150° and 155° C., which is about the melting point of the phenylhydrazin compound of glycuronic acid.

Conclusions. 1. The Cammidge reaction is a constant feature in hemorrhagic pancreatitis, in mechanical injuries of the gland (crushing of the tail, partial extirpation), and in total extirpation.

2. In certain cases of the subacute type of pancreatitis the reaction is inconstant.

3. The nature of the phenylhydrazin compound is not definitely established. If pentose, it is apparently not derived from the pentose-yielding material of the pancreas.

4. A positive reaction is indicative of altered carbohydrate metabolism due to disturbance of the internal secretion of the pancreas.

THE TONSILS AS ELIMINATIVE ORGANS.

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The true functions of the tonsils and other adenoid structures abutting on the mucous membranes is a problem nearly as obscure today as it was twenty years ago. They were then supposed to secrete a substance which facilitated swallowing the bolus of mas-